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(71) Applicant: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors: KLEINBART, Scott, N.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SHIROMANI, Prafull, K.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: NEW CYCLOBENZAPRINE COMPOSITION

(57) Abstract

Disclosed is a new pharmaceutical composition containing the skeletal relaxant, cyclobenzaprine. The composition also contains calcium dibasic phosphate hydrous, which provides a compressed tablet of the composition having improved hardness, friability (breakage) and dissolution properties.

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TITLE OF THE INVENTION

NEW CYCLOBENZAPRINE COMPOSITION

BACKGROUND OF THE INVENTION

Cyclobenzaprine, 5-(3-dimethylaminopropylidene)-dibenzo[a,e]cycloheptatriene, as the hydrochloride, is an extremely effective skeletal muscle relaxant and is sold as a 10 mg tablet under the tradename, FLEXERIL® by Merck & Co., Inc. Its pharmaceutical action involves relieving local skeletal muscle spasm without adversely interfering with muscle function.

A new 5 mg dosage form was required having greater bulk then the present commercial formulation for use as a core tablet in subsequent polymer coating or gelatin dipping. This necessitated a change in the nature of the present filler excipients, being hydroxypropylmethyl cellulose and hydroxypropyl cellulose.

Substitution with a commonly used filler excipient, microcrystalline cellulose, unexpectedly led to compressed tablets having poor hardness and friability (breakage) properties leading to chipping and cracking. Further, dissolution assays produced unexpectedly low values for drug content, indicating an undesirable chemical interaction between cyclobenzaprine and microcrystalline cellulose which occurred during tablet compression. This latter characteristic is of major concern since it can result in decreased drug bioavailability and potency.

Microcrystalline cellulose is listed in the "Handbook of Pharmaceutical Additives" by Michael and Irene Ash, 1995, Gower (England) as one of 93 different chemicals useful as fillers in pharmaceutical compositions.

What is desired is a pharmaceutically acceptable excipient formulation for producing cyclobenzaprine tablets having acceptable hardness, friability and dissolution properties (no chemical interaction between cyclobenzaprine and the excipient).

SUMMARY OF THE INVENTION

We have discovered that an acceptable tablet containing cyclobenzaprine and having acceptable hardness, friability and dissolution properties, can be produced by incorporating into the formulation, calcium phosphate dibasic hydrous, (also chemically referred to as calcium monohydrogen phosphate dihydrate) having the chemical formula, $CaHPO_4 \cdot 2H_2O$, as the excipient.

By this invention there is provided a composition comprising a pharmaceutically effective amount of cyclobenzaprine and calcium phosphate dibasic hydrous, as a pharmaceutically acceptable filler excipient.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The cyclobenzaprine can be present in a 5-10 mg quantity, and particularly 5 mg, taken as the free base. Preferably, it is present as the hydrochloride. Other useful pharmaceutically acceptable salts include the sulfate, acetate, and the like.

The pharmaceutical excipient, calcium phosphate dibasic hydrous, is present in an amount of 25 to 45 weight percent of the composition, and further useful amounts are 27-41% weight percent and 33-35% weight percent of the composition.

Other pharmaceutical excipients can also be present with calcium phosphate dibasic hydrous to modify, for example, hardness, friability, dissolution properties, color, sweetness, and the like, and are described and listed in "The Handbook of Pharmaceutical Additives", *supra*.

A sweetener/filler that can be used includes calcium saccharin, glycerin, dextrates, fructose, D-galactose, D-glucose monohydrate, honey, invert sugar, lactose, maltose, D-mannitol, and the like.

A useful sweetener/filler is lactose. A commercially useful form is lactose hydrous 80 Mesh.

The sweetener/filler can be present in an amount of 40 to 65 weight percent of the composition. A useful amount is 51-52 weight percent of the composition.

A binder/diluent/disintegrant can be used and includes: carrageenan, corn syrup solids, hydroxypropyl cellulose, polyvinyl acetate (homopolymers), Starch Pregelatinized (pregel starch), tristearin, and the like.

A useful binder/diluent is Starch Pregelatinized which can be present in an amount of 3 to 5 weight percent of the composition. A useful amount is 4 weight percent of the composition.

A lubricant can also be used in the composition and includes: magnesium stearate, calcium stearate, stearic acid, and the like.

A useful lubricant is magnesium stearate NF which can be present in an amount of 0.25 to 1.5 weight percent of the composition. A useful amount is 0.5 to 1.0 weight percent of the composition.

An additional excipient/filler can also be used in the composition. These include: calcium carbonate, cellulose acetate, butyrate, corn starch, dextrates, karaga gum, methyl cellulose, rapeseed oil, sucrose oleate, and the like.

A useful excipient/disintegrant is corn starch NF, which can be present in an amount of 3 to 5 weight present of the composition, and a useful amount being 4 weight percent of the composition.

A colorant can also be used to impart uniqueness in appearance, or alternatively, the tablet can be used with a white appearance.

Suitable colorants include FDA approved chemicals including DBC Blue No. 4, DBC Green No. 5, FD & C Red No. 40, yellow iron oxide, titanium dioxide (white), and the like.

A useful colorant is yellow Ferric oxide NF, which can be used in an amount of 0.01 to 0.1 weight percent of the composition. A useful amount is 0.03 to 0.05 weight percent of the composition.

The composition can be prepared by conventional methods in the art including simple mixing of the ingredients.

The composition can also be present in the form of a compressed tablet and prepared, for example, by the steps of: wet granulation using a high shear mixer, drying, utilizing a fluid bed dryer; particle size reduction in a homoloid mill; incorporation of magnesium stearate lubricant in a tumble blender; and compression utilizing a rotary tablet press. Following compression of a core tablet, it can be subsequently polymer coated with, e.g., hydroxypropyl cellulose, hydroxymethyl cellulose, or gelatin-dipped for ease in swallowing.

The following examples are illustrative of the invention and should not be considered to be limitations on the scope or spirit of the instant invention.

COMPARATIVE EXAMPLES

The following compositions I, II and III were prepared. However, they all suffered from poor hardness and friability resulting in breaking and chipping of the compressed tablet. Also they yielded low dissolution values in aqueous medium, indicating a chemical reaction between the cyclobenzaprine hydrochloride and microcrystalline cellulose had occurred. (N/A indicates "not applicable" since the ingredient was absent).

	I	II	III
Cyclobenzaprine HCl	5mg	5mg	5mg
Microcrystalline Cellulose	N/A	171mg	80mg
Lactose Hydrous NF	268.0mg	N/A	175mg
Starch Pregelatinized NF	58.4mg	170mg	96.3mg
Magnesium Stearate NF	2.31mg	1.00mg	3.50mg
Starch Corn NF	16.3mg	N/A	N/A
Yellow Ferric Oxide NF	N/A	0.15mg	0.15mg
Talc USP	N/A	2.10mg	N/A
Calcium Phosphate Dibasic Hydrous USP	N/A	N/A	N/A

EXAMPLE

The following composition was prepared by wet granulation process in which calcium phosphate dibasic hydrous was substituted for microcrystalline cellulose. The composition after mixing, was compressed into tablets using a conventional tablet machine, each having the following average composition (± 20%):

Cyclobenzaprine HCl	5 mg/tablet
Lactose Hydrous NF	227.0 mg/tablet
Pregel Starch 1551	18.0 mg/tablet
Magnesium Stearate NF	3.2 mg/tablet
Starch Corn NF	37.4 mg/tablet
Yellow Ferric Oxide NF	0.18 mg/tablet
Calcium Phosphate Dibasic Hydrous	148.2 mg/table

Sources of the materials used were:
Cyclobenzaprine HCl, (Merck & Co., Inc.)
Lactose Hydrous NF, (Foremost)
Starch Pregelatinized NF, (Colorcon)
Magnesium Stearate NF, (Mallinckrodt)
Starch Corm NF, (Corn Products)
Yellow Ferric Oxide NF, (Colorcon)
Calcium Phosphate Dibasic Hydrous USP, (Mallinckrodt)

The tablets exhibited acceptable hardness, friability and dissolution properties. No chemical interaction between the cyclobenzaprine and the excipient mixture was observed which would adversely affect the bioavailability of the cyclobenzaprine hydrochloride.

WHAT IS CLAIMED IS:

1. A composition comprising a pharmaceutically effective amount of cyclobenzaprine and calcium phosphate dibasic hydrous.

2. The composition of Claim 1 wherein said cyclobenzaprine is present in an amount of 5-10 mg.

3. The composition of Claim 1 where said calcium phosphate dibasic hydrous is present in an amount of 25 to 45 weight percent of the composition.

4. The composition of Claim 3 where said calcium phosphate dibasic hydrous is present in an amount of 27 to 41 weight percent of the composition.

5. The composition of Claim 4 where said calcium phosphate dibasic hydrous is present in an amount of 33 to 35 weight percent of the composition.

6. The composition of Claim 1 wherein said cyclobenzaprine is present as a pharmaceutically acceptable salt.

7. The composition of Claim 6 wherein said salt is the hydrochloride.

8. The composition of Claim 1 wherein said composition further contains a pharmaceutically acceptable excipient.

9. The composition of Claim 8 wherein said excipient is selected from the group consisting of lactose hydrous, starch pregelatinized, magnesium stearate and starch corn.

10. The composition of Claim 1 present as a compressed tablet.

11. The composition of Claim 1 comprising: cyclobenzaprine HCl, lactose hydrous 80 Mesh, starch pregelatinized, magnesium stearate, starch corn, yellow ferric oxide, and calcium phosphate dibasic hydrous.

12. The composition of Claim 11 comprising: cyclobenzaprine HCl, 5.0 mg.; lactose hydrous 80 Mesh, 227.0 mg; starch pregelatinized, 18.0 mg; magnesium stearate, 3.2 mg; starch corn, 37.4 mg; yellow ferric oxide, 0.18 mg; and, calcium phosphate dibasic hydrous, 148.2 mg.

13. The composition of Claim 12 present as a compressed tablet.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21598

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/20, 31/135
US CL :424/465; 514/654, 649

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/465; 514/654, 649

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

HCAPLUS- calcium phosphate dibasic hydrous as tablet excipient in compositions containg pharmaceutical actives including cyclobenzaprine.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,882,246 A (SHARE) 06 May 1975, see entire document, especially column 2.	1-13
Y	Database HCAPLUS on STN, American Chemical Society, AN 1976:566583, STAMM, A. et al. 'Compressibility of stable adjuvant substances for direct tabletting,' abstract, Acta Pharm. Technol., Suppl., 1976.	1-13
Y	Database HCAPLUS on STN, American Chemical Society, AN 1976:499123, OSSEEKEY et al. 'The use of magnesium lauryl sulfate in an insoluble direct compression tablet mix,' abstract, Pharm. Acta Helv., 1976.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database HCAPLUS on STN, American Chemical Society, AN 1972:37415, RIDGWAY et al. 'Properties of tablets made from direct-compression bases on an automatically controlled rotary machine,' abstract, J. Pharm., Pharmacol., 1971.	1-13